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Chapter 27: Nausea and Vomiting

INTRODUCTION

- Nausea is usually defined as the inclination to vomit or as a feeling in the throat or epigastric region alerting an individual that vomiting is imminent. Vomiting is defined as the ejection or expulsion of gastric contents through the mouth, often requiring a forceful event.
- Nausea, the imminent need to vomit, is associated with gastric stasis. Retching is the labored movement of abdominal and thoracic muscles before vomiting. The final phase of emesis is vomiting, the forceful expulsion of gastric contents due to GI retroperistalsis.
- Specific etiologies associated with nausea and vomiting are presented in **Table 27-1**.
- **Table 27-2** presents cytotoxic agents categorized by their emetogenic potential. Although some agents may have greater emetogenic potential than others, combinations of agents, high doses, clinical settings, psychological conditions, prior treatment experiences, and unusual stimuli to sight, smell, or taste may alter a patient's response to a drug treatment.

TABLE 27-1

Etiologies of Nausea and Vomiting

Intraperitoneal
- Mechanical obstruction
  - Gastric outlet obstruction
  - Bowel obstruction
- Altered sensorimotor function
  - Gastroparesis
  - Gastroesophageal reflux
  - Intestinal pseudo-obstruction
  - Irritable bowel syndrome
  - Chronic idiopathic nausea
  - Functional vomiting
  - Cyclic vomiting syndrome
  - Cannabinoid hyperemesis syndrome
  - Rumination syndrome
- Inflammatory diseases
  - Pancreatitis
  - Pyelonephritis
  - Cholecystitis
  - Appendicitis
  - Hepatitis
- Acute gastroenteritis
  - Viral
  - Bacterial
- Biliary colic
- Liver failure

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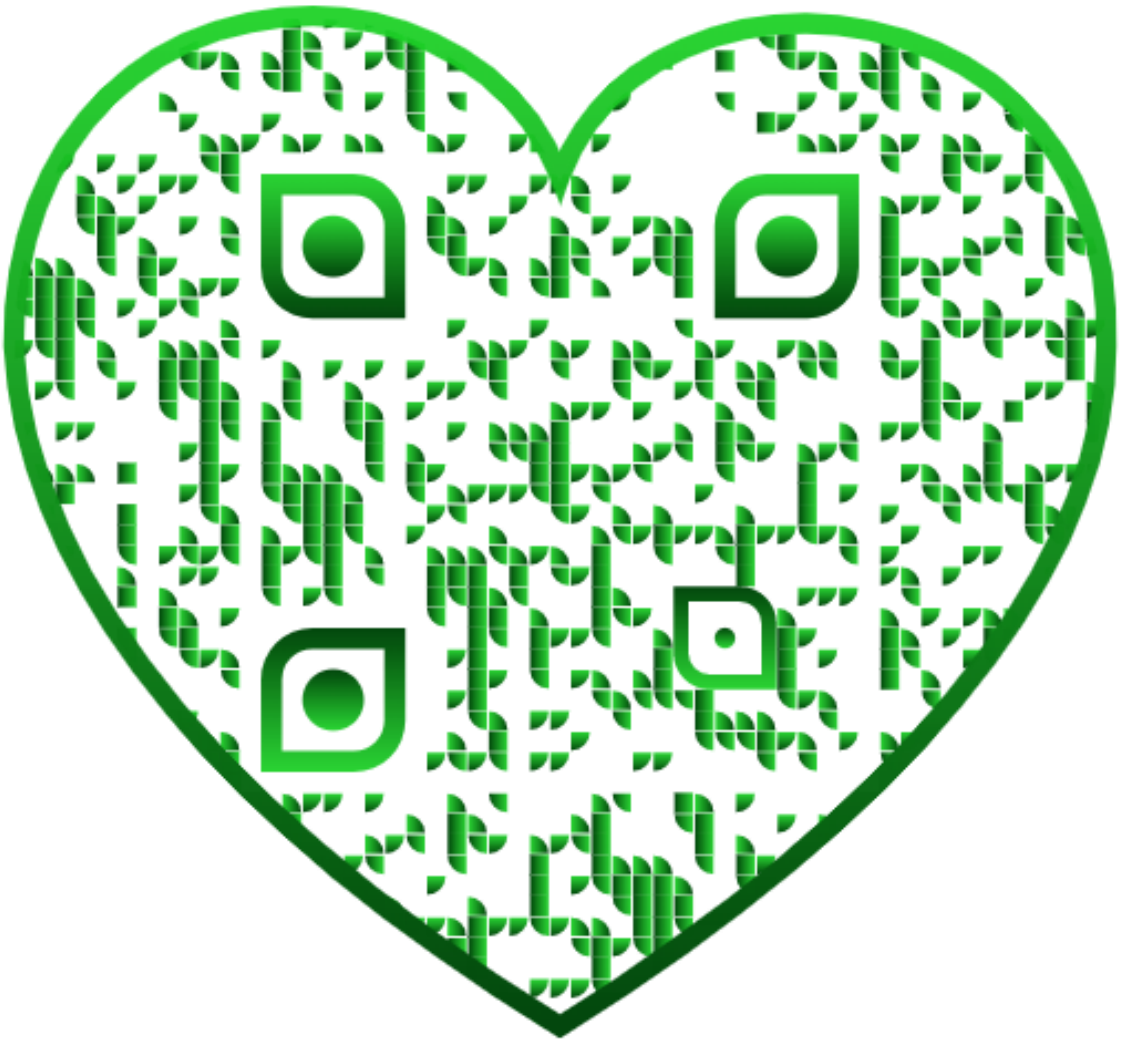

Cardiovascular Diseases
- Acute myocardial infarction
- Cardiomyopathy

Neurologic Processes
- Increased intracranial pressure
- Migraine headache
- Vestibular disorders
- Intracerebral hemorrhage
- Intracerebral malignancy

Metabolic Disorders
- Diabetes mellitus (diabetic ketoacidosis)
- Addison's disease
- Renal disease (uremia)

Psychiatric Causes
- Depression
- Anxiety disorders
- Anorexia and bulimia nervosa

Therapy-Induced Causes
- Antineoplastic agents
- Radiation therapy
- Anticonvulsant preparations
- Digoxin, cardiac antiarrhythmics
- Opioids
- Oral hypoglycemics
- Oral contraceptives
- Antibiotics
- Volatile general anesthetics
- Lubiprostone

Drug Withdrawal
- Opioids
- Benzodiazepines

Miscellaneous Causes
- Pregnancy
- Noxious odors
- Postoperative vomiting

TABLE 27-2

Emetic Risk of Agents Used in Oncology and Treatment Options

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Antiemetic Agent	Antiemetic Dose on Day 1 of Chemotherapy	Antiemetic Dose on Subsequent Days
High Risk (>90%): Anthracycline/Cyclophosphamide combination, Carmustine, Cisplatin, Cyclophosphamide > 1500 mg/m^2, Dacarbazine, Mechlorethamine, Streptozocin		
NK-1 Antagonist		
Aprepitant	125 mg oral or 130 mg IV	80 mg oral on days 2–3
Fosaprepitant	150 mg IV	
Netupitant-palonosetron	300 mg/0.5 mg oral	
Fosnetupitant-palonosetron	235 mg fosnetupitant/0.25 mg palonosetron IV	
Rolapitant	180 mg oral	
5-HT$_3$ Antagonist[a]		
Granisetron	2 mg oral or 1 mg IV or 10 mcg/kg IV or 1 patch or 10 mg SQ	
Ondansetron	24 mg oral or 8 mg IV or 0.15 mg/kg IV	
Palonosetron	0.5 mg oral	
Ramosetron	0.3 mg IV	
Tropisetron	5 mg oral OR 5 mg IV	
Dexamethasone[b]	12 mg or 20 mg oral/IV	8 mg oral/IV daily or twice daily on days 2–4
Olanzapine	5 mg or 10 mg oral	5 mg or 10 mg oral on days 2–4
Moderate Risk (30%–90%): Aldesleukin, Alemtuzumab, Arsenic trioxide, Azacitidine, Bendamustine, Busulfan, Carboplatin, Clofarabine, Cyclophosphamide < 1500 mg/m^2, Cytarabine > 1000 mg/m^2, Daunorubicin, Daunorubicin and cytarabine liposomal, Doxorubicin, Epirubicin, Fam-trastuzumab deruxtecan-nxki, Idarubicin, Ifosfamide, Irinotecan, Irinotecan liposomal injection, Oxaliplatin, Romidepsin, Temozolomide, Thiotepa, Trabectedin		
5-HT$_3$ Antagonist		
Granisetron	2 mg oral or 1 mg IV or 10 mcg/kg IV or 1 patch or 10 mg SQ	
Ondansetron	8 mg oral twice daily or 8 mg IV or 0.15 mg/kg IV	
Palonosetron	0.5 mg oral or 0.25 mg IV	
Ramosetron	0.3 mg IV	
Tropisetron	5 mg oral or 5 mg IV	

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Dexamethasone	8 mg oral/IV	8 mg oral/IV on days 2–3[c]
Low Risk (10%–30%): Aflibercept, Axicabtagene ciloleucel, Belinostat, Blinatumomab, Bortezomib, Brentuximab, Cabazitaxel, Carfilzomib, Cetuximab, Copanlisib, Cytarabine < 1000 mg/m^2, Decitabine, Docetaxel, Elotuzumab, Enfortumab vedotin-ejfv, Eribulin, Etoposide, Fluorouracil, Gemcitabine, Gemcitabine inotuzumab ixabepilone, Ixabepilone, Lanreotide, Methotrexate, Mitomycin, Mitoxantrone, Moxetumomab pasudotox, Nab-paclitaxel, Necitumumab, Nelarabine, Ozogamicin, Paclitaxel (conventional and albumin-bound), Panitumumab, Pegylated liposomal doxorubicin, Pemetrexed, Pertuzumab, Tagraxofusp-erzs, Topotecan, Trastuzumab emtansine, Vinflunine		
Choose One:		
5-HT$_3$ Antagonist		
Granisetron	2 mg oral or 1 mg IV or 10/kg IV or 1 patch or 10 mg SQ	
Ondansetron	8 mg oral or IV	
Palonosetron	0.5 mg oral or 0.25 mg IV	
Ramosetron	0.3 mg IV	
Tropisetron	5 mg oral or IV	
OR		
Dexamethasone	8 mg oral or IV	
Minimal Risk (<10%): Avelumab, Atezolizumab, Bevacizumab, Bleomycin, Cemiplimab, 2-Chlorodeoxyadenosine, Cladribine, Daratumumab, Durvalumab, Emapalumab, Fludarabine, Ipilimumab, Nivolumab, Obinutuzumab, Ofatumumab, Pembrolizumab, Pralatrexate, Ramucirumab, Rituximab (IV and SQ), Trastuzumab, Vinblastine, Vincristine (conventional and liposomal), Vinorelbine		
No routine prophylactic antiemetics are needed		

[a]No additional 5-HT$_3$-RA is needed if netupitant/palonosetron is used.

[b]Dexamethasone dose on day 1 should be reduced to 12 mg when given with aprepitant, fosaprepitant, and netupitant/palonosetron due to drug interactions. Dexamethasone dose on days 2–4 should be omitted when used as antiemetic with anthracycline/cyclophosphamide combination regimen or carboplatin AUC ≥ 4.

[c]Only if regimen is known to cause delayed nausea/vomiting (eg, cyclophosphamide, doxorubicin, oxaliplatin).

CLINICAL PRESENTATION

- The clinical presentation of nausea and vomiting is provided in **Table 27-3**. Nausea and vomiting may be classified as either simple or complex.
- **General**
  - ✓ Depending on severity of symptoms, patients may present in mild-to-severe distress
- **Symptoms**
  - ✓ *Simple:* Self-limiting, resolves spontaneously, and requires only symptomatic therapy

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✓ *Complex:* Not relieved after administration of antiemetics; progressive deterioration of patient secondary to fluid-electrolyte imbalances; usually associated with noxious agents or psychogenic events

- **Signs**
  - ✓ *Simple:* Patient complaint of queasiness or discomfort
  - ✓ *Complex:* Weight loss, fever, abdominal pain
- **Laboratory tests**
  - ✓ *Simple:* None
  - ✓ *Complex:* Serum electrolyte concentrations, upper/lower GI evaluation
- **Other information**
  - ✓ Fluid input and output
  - ✓ Medication history
  - ✓ Recent history of behavioral or visual changes, headache, pain, or stress
  - ✓ Family history positive for psychogenic vomiting

TABLE 27-3

Risk Factors for Postoperative Nausea and Vomiting (PONV)

Patient-Related Factors Age less than 50 years old Female gender (two to three times greater incidence of PONV vs males) Nonsmoker History of PONV or motion sickness (threefold increase in incidence of PONV) Hydration status
Factors Related to Anesthesia Use of general anesthesia Use of volatile anesthetics Nitrous oxide use for > 1 hour Use of opioids (intraoperative or postoperative)
Factors Related to Surgery Type of surgical procedure (highest risk: laparoscopic, gynecological, cholecystectomy) Duration of surgery: procedures lasting more than 1 hour

TREATMENT

- Goal of treatment: Prevent or eliminate nausea and vomiting; ideally accomplished without adverse effects or with clinically acceptable adverse effects.

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GENERAL APPROACH

- Treatment options for nausea and vomiting include drug and nondrug modalities. For patients who are suffering due to excessive or disagreeable food or beverage consumption, avoidance or moderation in dietary intake may lead to symptom resolution.
- Patients with symptoms of systemic illness may quickly improve as their underlying condition resolves. Patients in whom these symptoms result from labyrinthine changes produced by motion may benefit quickly by assuming a stable physical position.
- Nonpharmacologic interventions include relaxation, biofeedback, hypnosis, cognitive distraction, optimism, guided imagery, acupuncture, yoga, transcutaneous electrical stimulation, chewing gum, and systematic desensitization.
- Changes in diet such as restricting oral intake, eating smaller meals, avoiding spicy or fried foods and instead eating bland foods such as with the BRAT diet (Bananas, Rice, Applesauce, and Toast) can help alleviate symptoms.

PHARMACOLOGIC MANAGEMENT

- Information concerning commonly available antiemetic preparations is compiled in **Table 27-4**. The treatment of simple nausea and vomiting often involves self-care from a list of nonprescription products. Nonprescription and prescription drugs are useful in the treatment of simple nausea and vomiting in small, infrequently administered doses and are associated with minimal side effects.
- Factors that enable the clinician to choose the appropriate regimen include: (a) the suspected etiology of the symptoms; (b) the frequency, duration, and severity of the episodes; (c) the ability of the patient to use oral, rectal, injectable, or transdermal medications; and (d) the success of previous antiemetic medications.
- The management of complex nausea and vomiting, such as in patients who are receiving antineoplastic agents, may require initial combination therapy. In combination regimens, the goal is to achieve symptomatic control through administration of agents with different pharmacologic mechanisms of action.

TABLE 27-4

Common Antiemetic Preparations and Adult Dosage Regimens[a]

Drug	Adult Dosage Regimen	Dosage Form/Route	Availability
Antacids: Useful with simple nausea/vomiting *Adverse drug reactions: Magnesium products—diarrhea; Aluminum or calcium products—constipation*			
Antacids (various)	15–30 mL every 2–4 hours prn	Liquid/Oral	Nonprescription
Antihistaminic–Anticholinergic Agents: Especially problematic in the elderly; increased risk of complications in patients with BPH, narrow angle glaucoma, or asthma *Adverse drug reactions: Drowsiness, confusion, blurred vision, dry mouth, urinary retention*			
Dimenhydrinate (Dramamine)	50–100 mg every 4–6 hours prn	Tab, chew tab, cap	Nonprescription
Diphenhydramine (Benadryl)	25–50 mg every 4–6 hours prn 10–50 mg every 2–4 hours prn	Tab, cap, liquid IM, IV	Prescription/nonprescription
Hydroxyzine (Vistaril,	25–100 mg every 4–6 hours prn	Tab (unlabeled	Prescription

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Atarax)		use)	
Meclizine (Bonine, Antivert)	12.5–25 mg 1 hour before travel; repeat every 12–24 hours prn	Tab, chew tab	Prescription/nonprescription
Scopolamine (Transderm Scop)	1.5 mg every 72 hours	Transdermal patch	Prescription
Trimethobenzamide (Tigan)	300 mg three to four times daily 200 mg three to four times daily	Cap IM	Prescription
Benzodiazepine: Used for ANV but is contraindicated with olanzapine *Adverse drug reactions: Dizziness, sedation, appetite changes, memory impairment; observe for additive sedation especially if used with narcotic analgesics*			
Lorazepam (Ativan)	0.5–2 mg on night before and morning of chemotherapy	Tab, IV	Prescription (C-IV)
Butyrophenones: Used for breakthrough CINV; droperidol has limited use *Adverse drug reactions: Haloperidol—sedation, constipation, hypotension, EPS; droperidol—QTc prolongation and/or torsade de pointes, 12-lead electrocardiogram prior to administration, followed by cardiac monitoring for 2–3 hours after administration*			
Haloperidol (Haldol)	0.5–2 mg every 4–6 hours prn	Tab, liquid, IM, IV	Prescription
Droperidol (Inapsine)[b]	2.5 mg; additional 1.25 mg may be given	IM, IV	Prescription
Cannabinoids: Used for breakthrough CINV *Adverse drug reactions: Euphoria, somnolence, xerostomia*			
Dronabinol (Marinol)	5–15 mg/m^2 every 2–4 hours prn 4.2–12.6 mg/m^2 every 2–4 hours prn	Cap Oral solution	Prescription (C-III)
Nabilone (Cesamet)	1–2 mg twice daily	Cap	Prescription (C-II)
Corticosteroids: Useful as a single agent or in combination therapy for prophylaxis of CINV or PONV *Adverse drug reactions: Insomnia, GI symptoms, agitation, appetite stimulation, hypertension, and hyperglycemia*			
Dexamethasone	See **Table 27-2** for CINV dosing and **Table 27-3** for PONV dosing	Tab, IV	Prescription
Histamine (H2) Antagonists: Useful with nausea secondary to heartburn or GERD *Adverse drug reactions: Headache, constipation, or diarrhea*			

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Cimetidine (Tagamet HB)	200 mg twice daily prn	Tab	Nonprescription
Famotidine (Pepcid AC)	10 mg twice daily prn	Tab	Nonprescription
Nizatidine (Axid AR)	75 mg twice daily prn	Tab	Nonprescription
5-Hydroxytryptamine-3 Receptor Antagonists: Useful as a single-agent or combination therapy for prophylaxis of CINV or PONV *Adverse drug reactions: Asthenia, constipation, headache*			
	See **Table 27-2** for CINV dosing and **Table 27-3** for PONV dosing	Tab, IV	Prescription
Miscellaneous Agents **Metoclopramide:** Prokinetic activity useful in diabetic gastroparesis. *Adverse drug reactions: Asthenia, headache, somnolence, EPS* **Amisulpride:** Mainly used in PONV; avoid use in severe renal impairment. *Adverse drug reactions: Increased serum prolactin, prolonged QTc interval* **Olanzapine:** Use with caution in elderly; contraindicated with benzodiazepines. *Adverse drug reactions: Sedation, prolonged QTc interval, EPS* **Pyridoxine:** Used in NVP. May be used alone or in combination with doxylamine 12.5 mg. Combination product available as prescription. *Adverse drug reactions: Drowsiness, headache*			
Metoclopramide (Reglan)	10–20 mg (0.5–2 mg/kg) four times daily	Tab, IV	Prescription
Olanzapine (Zyprexa)	5–10 mg daily	Tab	Prescription
Pyridoxine (vitamin B_6)	10–25 mg orally three to four times daily	Tab, cap	Nonprescription
Amisulpride	5–10 mg once either before or after surgery	Tab	Prescription
Phenothiazines: Useful in simple nausea/vomiting or breakthrough CINV *Adverse drug reactions: Prolonged QTc interval, constipation, dizziness, tachycardia, tardive dyskinesia, drowsiness*			
Chlorpromazine (Thorazine)	10–25 mg every 4–6 hours prn	Tab, liquid	Prescription
	25–50 mg every 4–6 hours prn	IM, IV	
Prochlorperazine (Compazine)	5–10 mg every 4–6 hours prn	Tab, liquid	Prescription

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	5–10 mg every 3–4 hours prn	IM	
	2.5–10 mg every 3–4 hours prn	IV	Prescription
	25 mg twice daily prn	Supp	Prescription
Promethazine (Phenergan)	12.5–25 mg every 4–6 hours prn	Tab, liquid, IM, IV, supp	Prescription
Substance P/Neurokinin-1 Receptor Antagonist: Useful in combination therapy for prophylaxis of CINV and PONV *Adverse drug reactions: Constipation, diarrhea, headache, hiccups, dyspepsia, and fatigue*			
Aprepitant	See **Table 27-2** for CINV dosing and **Table 27-5** for PONV dosing	Cap, IV	Prescription
Fosaprepitant		IV	Prescription
Fosnetupitant-palonosetron		IV	Prescription
Netupitant/Palonosetron		Cap	Prescription
Rolapitant		Cap	Prescription

ANV, anticipatory nausea and vomiting; C-II, C-III, and C-IV, controlled substance schedule 2, 3, and 4, respectively; cap, capsule; chew tab, chewable tablet; CINV, chemotherapy-induced nausea and vomiting; GERD, gastroesophageal reflux disease; liquid, oral syrup, concentrate, or suspension; PONV, postoperative nausea and vomiting; prn, as needed; supp, rectal suppository; tab, tablet.

[a]All regimens should be monitored for resolution or occurrence of nausea and vomiting as well as maintaining an adequate hydration status.

[b]See text for warnings.

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TABLE 27-5

Recommended Prophylactic Doses of Selected Antiemetics for Postoperative Nausea and Vomiting in Adults and Postoperative Vomiting in Children

Drug	Adult Dose	Pediatric Dose (IV)	Timing of Dose[a]
Amisulpride	5 mg	Not included in consensus guidelines	At induction
Aprepitant	40 mg orally	3 mg/kg up to 125 mg	At induction
Dexamethasone	4–8 mg IV	150 mcg/kg up to 5 mg	At induction
Dimenhydrinate	1 mg/kg IV	0.5 mg/kg up to 25 mg	Not specified
Droperidol[b]	0.625 mg IV	10–15 mcg/kg up to 1.25 mg	At end of surgery
Granisetron	0.35-–3 mg IV	40 mcg/kg up to 0.6 mg	At end of surgery
Haloperidol	0.5–2 mg (IM or IV)	Not included in consensus guidelines	Not specified
Methylprednisolone	40 mg IV	Not included in consensus guidelines	Not specified
Metoclopramide	10 mg	Not included in consensus guidelines	Not specified
Ondansetron	4 mg IV, 8 mg orally or orally disintegrating tablet	Age ≥ 1 month: 50–100 mcg/kg up to 4 mg	At end of surgery
Palonosetron	0.075 mg IV	0.5–1.5 mcg/kg	At induction
Promethazine[b]	6.25 mg IV	Not included in consensus guidelines	At induction
Ramosetron	0.3 mg IV	Not included in consensus guidelines	At end of surgery
Rolapitant	70–200 mg orally	Not included in consensus guidelines	At induction
Scopolamine	Transdermal patch	Not included in consensus guidelines	Prior evening or 24 hours before surgery
Tropisetron	2 mg IV	0.1 mg/kg up to 2 mg	At end of surgery

[a]Based on recommendations from consensus guidelines.

[b]See FDA “black box” warning.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

- There are five categories of CINV: acute, delayed, anticipatory, breakthrough, and refractory. Nausea or vomiting that occurs within 24 hours of chemotherapy administration is defined as acute CINV, whereas when it starts more than 24 hours after chemotherapy administration, it is defined as delayed CINV.

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- Nausea or vomiting that occurs prior to receiving chemotherapy is termed anticipatory nausea and vomiting (ANV). Breakthrough nausea and vomiting occurs in 10%–40% treated with antiemetics and is defined as emesis occurring despite prophylactic administration of antiemetics and requiring the use of rescue antiemetics.
- Refractory nausea and vomiting is evident when there is a poor response to antiemetic regimens in prior cycles of chemotherapy.
- The emetogenic potential of the chemotherapeutic agent or regimen (see **Table 27-2**) is the primary factor to consider when selecting an antiemetic for prophylaxis of CINV. Recommendations for antiemetics in patients receiving chemotherapy are presented in **Table 27-2**.

Prophylaxis of CINV

- The primary goal of emesis prevention is no nausea and/or vomiting throughout the period of emetic risk.
- The duration of emetic risk is 2 days for patients receiving moderately emetogenic chemotherapy and 3 days for highly emetogenic chemotherapy. Emetic prophylaxis should be provided through the entire period of risk.
- The selection of the antiemetic regimen should be based on the chemotherapy drug with highest emetogenicity (see **Table 27-2**). Prior emetic experience and patient-specific factors should also be considered.
- When given in equipotent doses, oral and IV 5-HT3-RAs are equivalent in efficacy.
- The toxicities of antiemetics should be considered and managed appropriately.

RADIATION-INDUCED NAUSEA AND VOMITING

- RINV occurs in approximately one-third of patients, is site dependent, and can have a substantial impact on a patient's quality of life. Risk factors associated with the development of RINV include combination chemoradiotherapy, prior CINV, upper abdomen RT, and field size.
- For information on treatment options for the prevention of RINV, see Chapter 155, "Supportive Care" in Pharmacotherapy: A Pathophysiologic Approach, 13th edition.

POSTOPERATIVE NAUSEA AND VOMITING (PONV)

- Risk factors for PONV are listed in **Table 27-3**. Patients with multiple risk factors are at highest risk for PONV. In adults with 0, 1, 2, 3, and 4 of the risk factors the incidence of PONV is 10%, 20%, 40%, 60%, and 80%, respectively. Those who are found to have zero to one risk factors are considered low risk, those with two risk factors are considered medium risk, and those with three or more risk factors are considered high risk.
- A variety of pharmacologic approaches are available and may be prescribed as single or combination therapy for prophylaxis of PONV. See **Table 27-3** for doses of specific agents. **Ondansetron** is considered the "gold standard" 5-HT3-RA and has the most data supporting its use at the end of surgical procedures. However, it is less effective than longer-acting agents such as aprepitant, ramosetron, granisetron, and fosaprepitant in decreasing emesis beyond 24 hours and less effective than palonosetron in decreasing the incidence of PONV.
- Patients at highest risk of vomiting (>2 risk factors) should receive three or four prophylactic antiemetics from different pharmacologic classes, while those at moderate risk (1–2 risk factors) should receive a two-drug regimen. The combination of a 5-HT3-RA plus dexamethasone 4 to 8 mg is considered the cornerstone of therapy. For prophylaxis of PONV **scopolamine patches** must be initiated the evening before the surgery or at least 2 hours prior, whereas NK1 antagonists should be given during the induction of anesthesia; all other agents are recommended to be given at the end of the surgery.
- Patients who experience PONV after receiving prophylactic treatment with a combination of 5-HT3-RA plus **dexamethasone** should be given rescue therapy from a different drug class such as a phenothiazine, metoclopramide, or droperidol. If no prophylaxis was given initially, the recommended treatment is **ondansetron** 4 mg orally or IV or **ramosetron** 0.3 mg IV.

DISORDERS OF BALANCE

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- Beneficial therapy for patients with nausea and vomiting associated with disorders of balance can reliably be found among the antihistaminic–anticholinergic agents. Oral regimens of antihistaminic–anticholinergic agents given one to several times each day may be effective, especially when the first dose is administered prior to motion.
- **Scopolamine** (usually administered as a patch) is effective for the prevention of motion sickness and is considered first line for this indication.

ANTIEMETIC USE DURING PREGNANCY

- A prenatal vitamin started 1 month prior to becoming pregnant may help reduce the incidence and severity of nausea and vomiting of pregnancy (NVP). Eating smaller, more frequent meals every 1–2 hours, and avoiding foods or odors that trigger symptoms is recommended.
- **Pyridoxine** (10–25 mg one to four times daily) is recommended as first-line therapy with or without doxylamine (12.5–20 mg one to four times daily). **Dimenhydrinate, diphenhydramine, prochlorperazine,** or **promethazine** may also be considered in the treatment of NVP.
- Patients with persistent NVP or who show signs of dehydration should receive IV fluid replacement with thiamine then dextrose.
- **Ondansetron, promethazine**, and **metoclopramide** have similar effectiveness for hyperemesis gravidarum, although ondansetron may be better tolerated due to less adverse effects.

See Chapter 56, Nausea and Vomiting, authored by Leigh Anne Hylton Gravatt, Krista L. Donohoe, and Anne M. Masich, for a more detailed discussion of this topic.

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